REMARKS

Claims 1-21, 23-44 and 75-94 are pending in the instant application.

Claims 22 and 45-74 were previously canceled without prejudice or disclaimer.

Claims 16 and 17 are cancelled herewith. Claims 1, 23, 28 and 34 have been amended to incorporate the limitations of these cancelled claims. Applicants reserve the right to pursue to subject matter of the claims as originally presented in one or more continuing applications.

Process claims 23-44 were previously withdrawn from consideration, Applicants reserve the right to rejoin the withdrawn process claims upon the allowance of one or more of the product claims from which they depend (MPEP §821.04).

Applicants acknowledge the Examiner's withdrawal of the following rejections:

(i) rejection of Claims 1-3, 8-11, 14-19, 22, 77-81, 84 and 86-94 under 35 U.S.C. § 102(a) in view of Park et al. (Nucleic Acids Research Supplement (2001), No. 1, pp. 219-20);

(ii) rejection of Claims 1-3, 8-11, 14-22, 77-81, 84 and 86-94 under 35 U.S.C. § 102(e) in view of McSwiggen et al. (US 2003/0175950A1); and

(iii) rejection of claim 22 under 35 USC §112, first paragraph, for allegedly failing to comply with the written description requirement.

With respect to the remaining rejections, Applicants respectfully request reconsideration and examination of this application and the timely allowance of the pending claims in view of the arguments presented below.

Claim Rejections -35 USC §103

The Examiner has maintained the rejection of claims 1-11, 14-21, 75-84 and 86-94 under 35 U.S.C. § 103(a) for alleged obviousness over Draper et al. (US Patent No. 5,693,535; filed August 13, 1997; granted October 26, 1999) in view of Tuschl et al. (US Patent No. 7,056,704; filed April 27, 2004; granted June 6, 2006). The rejection of claims 12, 13 and 85 under 35 U.S.C. §103(a) over Draper et al. and Tuschl et al. and further in view of Svoboda et al. (Biochem. Biophys. Res. Comm., 287: 1099-1104 (2001)) have also been maintained (see page 4 of Office Action). Specifically, the Examiner maintains that "it would have been obvious to

one of ordinary skill in the art at the time of the invention to substitute the siRNAs of Tuschl for the ribozymes of Draper when targeting HIV for degradation" (see page 3 of Office Action).

Applicants traverse the rejection and maintain that the skilled artisan at the time of the invention would not have substituted the non-analogous ribozyme art of Draper et al. with the siRNA art of Tuschl et al. in order to arrive at the claimed invention. According to the Examination guidelines set forth by the Office (MPEP 2143, §B), the rationale that a claim is obvious based on the substitution of one known element for another can only be made if the results of the substitution would have been predictable. Applicants submit that the allegedly simple substitutions relied upon by the Examiner would not have yielded predictable results to one of ordinary skill in the art. In particular, Applicants maintain their position that the skilled artisan would have had no reasonable expectation of success in substituting the ribozyme technology of Draper et al. with the siRNA of technology of Tuschl et al. to mediate RNA interference (RNAi) of the viral RNA genome of an RNA virus such as HIV.

In maintaining the instant rejection, the Examiner has disputed the unexpected nature of the invention on three grounds (see page 6 of Office Action). First, the Examiner contends that "there is no evidence of record that HIV genomic RNA in nucleocapsid form is as inaccessible to siRNA as RSV genomic RNA". Second, the Examiner alleges that "since nucleocapsid proteins must be removed from the genomic RNA during replication to allow reverse transcriptase access to the template...one would reasonably expect the genome to be vulnerable to siRNA", particularly in view of observations by Park et al. (Nucleic Acids Supplement (2001), No. 1 pp. 219-220) that long dsRNAs inhibited HIV replication in COS cells. Third, the Examiner contends that "there is no reason of record to believe that siRNAs would not inhibit HIV gene expression from integrated proviral genomes which are expressed in the absence of the nucleocapsid".

With respect to the Examiner's first ground, Applicants respectfully submit that they are unaware of any direct evidence that HIV genomic RNA is inaccessible to siRNA. Indeed, Applicants' invention provides objective evidence that precisely the opposite is true. Nevertheless, it is Applicants' contention that the claimed invention was surprising and unexpected in view of published reports that the genomic RNA of a related RNA virus (i.e., RSV) is resistant to RNAi cleavage due to its tight association with nucleocapsid protein (see, e.g., Bitko V. & Barik S., *BMC Microbiol.*, 1:34-45 (2001), made of record in Applicant's

previous response). Given these findings, one skilled in the art would have had every reason to expect that the genomic RNA of the related HIV virus would be also be inaccessible to siRNA.

Applicants also disagree with the Examiner's assertion than the skilled artisan (prior to the instant invention) would have reasonably expected the genomic RNA of HIV to be particularly vulnerable to siRNA cleavage during its reverse transcription. Applicants respectfully submit that the opposite would have been expected prior to Applicant's invention. It is well known in the art that upon HIV-1 infection, genomic viral RNA is introduced into the host cell cytoplasm in the form of a nucleoprotein complex or "core" comprising viral proteins (including HIV reverse transcriptase) which are tightly associated with genomic viral RNA (see Moore and Stevenson; reference C21 in IDS filed 7/16/07). It is within this complex that the viral reverse transcriptase enzyme directs the synthesis of viral cDNA intermediates from the genomic viral RNA template. Since viral cDNA synthesis occurs as the complex transits the cytoplasm of the host cell, one skilled in the art would have reasonably expected the HIV nucleoprotein complex to have evolved defense mechanisms to prevent cellular degradation of its genetic material. This is supported by Tanchou et al., J. Mol. Biol., (1995) 252: 563-571 (attached herewith as Exhibit A), who found that while nucleoprotein complexes promote reverse transcription, they also protect the genomic RNA against degradation by exogenous nucleases. Given the protective role of the nucleoprotein complex, one skilled in the art would have expected virion-associated or "incoming" genomic RNA to be refractory to cleavage by RISC endonuclease complexes containing complementary siRNAs. Thus, Applicants' demonstration that siRNA can in fact cleave incoming genomic RNA is clearly surprising and unexpected.

Applicants' invention has important implications for the treatment of HIV. Unlike other gene silencing agents which solely target the many thousands of viral mRNA transcripts synthesized from an productively infected cell, the siRNAs of the invention can effectively prevent establishment of a productive infection by cleaving the few copies of incoming genomic HIV RNA before they can be reverse transcribed to form a HIV provirus that irreversibly integrates into the host cell chromosome. Although the siRNAs of the invention may also be capable of cleaving the many thousands of genomic viral RNA copies that are synthesized following proviral integration (as the Examiner suggests), the fact that they are also capable of preventing proviral integration and establishment of infection greatly improves their feasibility

as effective HIV therapeutics. Applicants have amended the claims to highlight this important feature.

Finally, Applicants submit that the Park et al. reference (Park et al., Nucleic Acids Research Supplement (2001), No. 1, p. 219-20) provides no basis on which to question the unexpected nature of the claimed invention. The data provided by Park et al. can best be considered sparse. Park et al. provide a single figure (Figure 2) which allegedly demonstrates that long dsRNA can inhibit the production of HIV virus from a plasmid template. The data in Figure 2 are the results of an experiment in which COS cells were cotransfected with long dsRNAs and proviral HIV DNA in the form of a plasmid (pNL4-3). Accordingly, the experiment is intended to assay the effects of long dsRNAs during the late stages of the HIV infection cycle (i.e., following proviral integration) when productive infection is already underway. Park et al. provide no evidence to suggest to one of skill in the art that long dsRNAs (much less siRNAs) can effectively interfere with earlier stages of the infection cycle that precede the integration of the provirus. Accordingly, the skilled artisan relying on Park et al. would not have predicted that siRNAs are capable of cleaving incoming genomic RNA.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) for alleged obviousness be reconsidered and withdrawn.

CONCLUSION

In view of the above amendment and response, Applicants believe the pending application is in condition for allowance. Nevertheless, if a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney, Debra J. Milasincic, Esq., at (617) 227-7400.

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Respectfully submitted,

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